

HIV Elite Controllers – the Issue at Heart

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ABSTRACT

Background: People with HIV are living longer, and as this population ages, chronic diseases associated with ageing, such as cardiovascular disease, will become of great importance (3). Elite controllers (EC) are a small subset of the HIV population, who maintain viral suppression below the limit of detection in the absence of antiretroviral therapy. Despite non-medical viral control and the absence of HIV-related opportunistic infection, there is concern that their protective immune activation places them at greater risk for coronary atherosclerosis, compared to their medically controlled viremic counterparts (1).

Objective: To summarize literature in a systematic fashion to collect evidence pointing to an association between elite controller status and increased risk of coronary atherosclerosis.

Methods: A structured literature review was conducted using three databases: Scopus, PubMed and Web of Science. The findings were restricted to journal articles and reviews published from 2005-2016. Keywords used for the search were “elite” AND “controller” AND “coronary” OR “cardio”. A total of 4 articles were selected based on the keywords. Article references were screened to include two more articles. The references from those were screened for a total of 6 articles meeting inclusion and exclusion criteria.

Results: Upon review of the articles, two supported the claim that ECs have a higher risk of coronary atherosclerosis than medically controlled HIV viremic patients, one shows no association. Three articles were inconclusive, two because of mixing of results for ECs with viremic controllers (another subpopulation of HIV patients) and one requiring further follow-up.

Conclusion: The findings suggest that there may be an association between HIV EC status and an increased risk of coronary atherosclerosis compared to medically controlled HIV patients, however, further studies are required in order to confirm this association.

INTRODUCTION

WHO ARE ELITE CONTROLLERS?

Elite Controllers (EC) are a rare and unique subset of the HIV population representing less than 1% of all HIV-infected individuals. This group of HIV “nonprogressors” is defined by their ability to maintain an undetectable viral load using clinical assays (HIV RNA <50 copies/mL) without the use of antiretroviral therapy (7). The mechanism for this viral control is still unknown (1). This spontaneous control of HIV has been subject to investigation for a potential “functional cure” of HIV; control of viral replication without the use of antiretroviral therapy (8).

WHY IS CORONARY ATHEROSCLEROSIS A CONCERN IN THIS POPULATION?

Despite their apparent ability to control the HIV virus, studies have found evidence to suggest ECs exhibit ongoing inflammation due to chronic immune activation and low level viral replication. This may carry a higher risk for inflammation-associated vascular dysfunction when compared to HIV-uninfected individuals (7).

OBJECTIVE:

This structured literature review will investigate the association between EC and coronary atherosclerosis, one of the most prevalent forms of heart disease and a leading cause of death (9). These findings may be used to evaluate standards of care and may suggest treatment to improve the prognosis of ECs.

RESEARCH QUESTION:

Do HIV-elite controllers have a higher risk of coronary atherosclerosis than medically controlled HIV viremic patients?

REFERENCES

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8. A. B. Desousa, B. Avettand-Fenouil, V. & Rouziou, C. Elite controllers as a model of functional cure. *Curr. Opin. HIV AIDS* 6, 181-187 (2011).
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RESULTS

Study	Study Type	Population	Purpose	Preliminary Findings	Conclusions	Limitations	Association
Crowell et al. (2016)	Prospective Cohort	<ul style="list-style-type: none"> 33/188 HIV controllers (elite/viremic) 89% male, median: 27yo at diagnosis, <1 year post-infection 870 HIV-viremic, 94% male, median: 29yo at diagnosis, majority 1-3yrs post-infection 	To characterize the rates and reasons for hospitalization among HIV Controllers and persons with medically-controlled HIV in a cohort of HIV-infected U.S. military personnel and beneficiaries.	<ul style="list-style-type: none"> Fewer hospitalizations among elite controllers as compared to viremic controllers. 	<ul style="list-style-type: none"> No significant difference in hospitalization rate between HIV controllers and HIV viremic patients. Determined: incidence 	<ul style="list-style-type: none"> The study was not adequately powered to detect differences in hospitalization rates between ECs and HIV-viremic patients. Could not compare viremic to elite control patients. Patient population may have been too young to detect a difference in hospitalization rates due to cardiovascular disease. Study only included young and healthy military personnel. 	INCONCLUSIVE
Crowell et al. (2015)	Retrospective Cohort	<ul style="list-style-type: none"> 149 ECs, Median: 46yo, 49% M 4,709 HIV+ (ART), Median: 45yo, 74% M 7,998 HIV+ low viremia, median: 44yo, 74% M 10,605 HIV+ high viremia, median: 40yo, 69% M All patients were immunologically intact 	To use a multisite, multistate cohort of HIV patients to compare hospitalization rates among ECs with those of HIV+ patients with medically controlled and uncontrolled HIV.	<ul style="list-style-type: none"> ECs had the highest all-cause hospitalization of all groups, with higher hospitalization than those in medical control. Cardiovascular disease was the most common reason for admissions overall but was more common among elite controllers, accounting for >30% of admissions. 	<ul style="list-style-type: none"> Increased rate of hospitalization of EC patients compared to HIV+ medically controlled patients. ECs had higher rates of hospitalization due to cardiovascular events. Cardiovascular hospitalization was the most common cause for ECs. Determined: incidence 	<ul style="list-style-type: none"> Potential for selection bias owing to data being limited to persons actively engaged in HIV care. Because ECs don't use ART, the study may have only captured those ECs with additional serious medical conditions. Lack of data on smoking. 	YES
Krishnan et al. (2014)	Experimental	<ul style="list-style-type: none"> 68 ECs, Median: 47yo, median time from diagnosis: 14 years 68 HIV-viremic (ART), median: 46yo, median time from diagnosis: 10 years 35 HIV-negative, median: 33yo Controlled for smoking, comorbidities 	<ul style="list-style-type: none"> To observe for a significant increase in inflammatory biomarkers in ECs compared to HIV viremic, and HIV-negative controls. To observe for an increase in monocyte activation in ECs which are associated with migration to atherosclerotic plaques impacting its progression towards rupture. 	<ul style="list-style-type: none"> Observed a significant increase in inflammatory biomarkers in ECs compared to HIV+ and HIV-negative controls. Observed an increase in monocyte activation in ECs which are associated with migration to atherosclerotic plaques, impacting its progression towards rupture. 	<ul style="list-style-type: none"> Abnormality of both inflammatory and coagulation soluble biomarkers and monocyte subsets in ECs. Rates were similar or higher than those observed in HIV-viremic, and HIV-negative controls. Determined: risk 	<ul style="list-style-type: none"> Requires further study to consider clinical implications. The incidence of cardiovascular events is low, therefore longitudinal studies with a larger number of participants will be required to further evaluate the clinical implications of these findings. 	INCONCLUSIVE
Lucero et al. (2013)	Prospective Cohort	<ul style="list-style-type: none"> 574 HIV viremic, median: 43yo, 80% M 64 ECs 76 viremic controllers 434 non-controllers (HIV+) 	To determine whether the reduction of the risk of the appearance of new non-AIDS events with ART depends on the level of immunosuppression reached. Should nonprogressors and ECs be started on ART early.	<ul style="list-style-type: none"> Incidence rates of non-AIDS events was similar in ECs, viremic controllers, and noncontrollers. 	<ul style="list-style-type: none"> Suggestive that early initiation of ART could prevent the appearance of new non-AIDS events in controllers. Determined: crude incidence 	<ul style="list-style-type: none"> Small sample size. Non-AIDS events were not clearly defined Criteria of selecting patients for non-AIDS events were only by admission to inpatient ward. Excluded clinic visits. Results were combined for viremic and elite controllers. Did not control for comorbid factors, smoking, hypertension etc. 	INCONCLUSIVE
Pereyra et al. (2013)	Cross-Sectional	<ul style="list-style-type: none"> 10 ECs, 40-60yo, 80% M (ART-naive) Controls: Chronic HIV+ and HIV-negative patents 	To determine the contribution of immune activation to the increased atherosclerotic disease of HIV-infected patients.	<ul style="list-style-type: none"> No difference in plaques between HIV-1 chronic, and HIV-negative patients. Plaques were increased in ECs compared to HIV-negative control. Coronary vessel stenosis was greater in ECs than in HIV-1 chronic controls. 	<ul style="list-style-type: none"> Observed a contribution of immune activation to the increase in atherosclerotic disease of HIV-infected patients. Determined: prevalence 	<ul style="list-style-type: none"> Small sample size Measurement of cardiovascular disease risk was cross-sectional. 	YES
Hsue et al. (2009)	Cross-Sectional	<ul style="list-style-type: none"> 33 ECs (VL<75), median: 44yo, 70% M, 42% Caucasian 93 HIV-neg, median: 49yo, 77% M, 60% Caucasian 96 HIV+ ART naive (VL>75), median: 45yo, 89% M, 68% Caucasian 180 HIV+ ART+ (VL<75), median: 49yo, 88% M, 68% Caucasian 92 HIV+ ART+ (VL>75), median: 47yo, 90% M, 50% Caucasian. Overall: 13.25yrs since diagnosis 	To consider the contribution of ART therapy, inflammation, and immunodeficiency on HIV-associated atherosclerosis.	<ul style="list-style-type: none"> Carotid intima-media thickness (IMT) and C-Reactive Protein (CRP) were higher in all HIV patients compared to HIV-negative controls. ECs weren't on ART, had no immunodeficiency, or viremia, but still had higher IMT and CRP levels than other HIV patients. 	<ul style="list-style-type: none"> ECs had a higher IMT thickness than all other groups. ECs had an equally elevated CRP as other HIV+ groups even though they lack ART, immunodeficiency, and viremia. Determined: risk 	<ul style="list-style-type: none"> Cross-sectional studies cannot measure the progression of carotid IMT thickness. There is an absence of studies correlating carotid IMT with cardiovascular event rates in the HIV infected population. HIV seronegative patients may have unmeasured confounders such as an unusually low IMT that could have differed from the HIV population. 	NO

METHODS

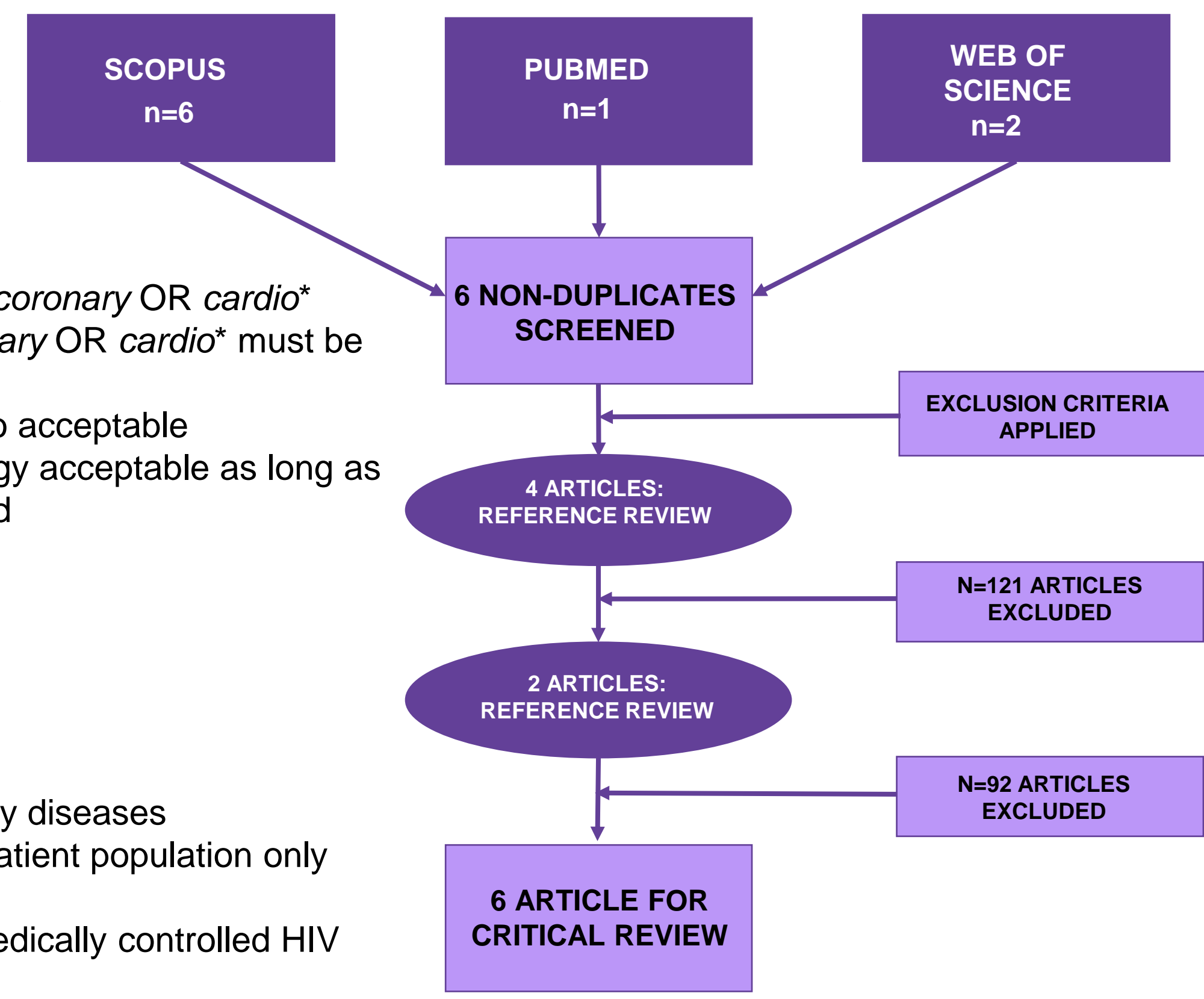
A search of three databases, was conducted from the dates of September 28th 2016 to November 9th 2016. The databases included SCOPUS, PubMed and Web of Science. The structured literature review was conducted in the same manner for each database, using the same inclusion and exclusion criteria. Terms were searched for in the title, abstract, and keywords, and included “elite” AND “controller” AND “coronary” OR “cardio”. Using SCOPUS as an example: these terms resulted in six matches. Exclusion criteria were applied to result in four acceptable articles. References were reviewed and two more articles were found that met the inclusion criteria. References were reviewed for those articles to exclude non-qualifying articles. The reference search did not produce any new leads. Six articles were analyzed by two investigators. Each investigator had the same items of focus, and comparisons were later conducted to determine the final conclusion.

Inclusion criteria

- elite AND controller AND coronary OR cardio*
- elite controller AND coronary OR cardio* must be present in body of article
- Term: atherosclerosis also acceptable
- Other controller terminology acceptable as long as elite controller was defined
- Published: 2005-2016
- English language only
- Article OR Review

Exclusion criteria

- Viremic controller
- Long-term nonprogressor
- Other chronic inflammatory diseases
- Assessment of non-HIV patient population only
- Article not peer reviewed
- Did not compare EC to medically controlled HIV population



DISCUSSION

- 2 of 6 studies linked HIV EC status with an increased risk of coronary atherosclerosis, compared to medically controlled HIV patients; one showed no increase in risk; while 3 were inconclusive.
- Lucero et al. (2013) was inconclusive due to the mixing of two HIV populations: ECs and viremic controllers. Krishna et al. (2014) could not link study results to clinical implications, and Crowell et al (2016) did not have adequate power to differentiate the hospitalization rates of ECs from other HIV populations.
- The two affirmative studies were observing a different rate (risk, incidence, or prevalence), and the positive results give greater weight to our hypothesis, however, as the inconclusive and contradictory results indicated, further testing is required to confirm these findings.
- The difficulty of enrolling ECs into studies due to their independence from ART was indicated by Crowell (2015), and could be the primary reason many studies have difficulty confirming a causal link between HIV EC status and atherosclerosis.
- There was conflicting information about the hospitalization rates among ECs
- The study with no association did indicate an increased risk of atherosclerosis in HIV EC patients compared to non-medically controlled HIV patients, however the risk was negligible compared to medically controlled HIV patients.
- There was overall consensus in the three studies measuring inflammation that ECs have a greater amount of inflammation than their HIV+ and HIV-negative counterparts.
- ECs are rare in the HIV cohort and may be underrepresented due to not seeking care, unlike their HIV viremic counterparts.



CONCLUSION

- There may be an association between ECs and an increase in risk of coronary atherosclerosis compared to individuals with medically controlled HIV.
- It is evident that ECs are at a greater risk for coronary atherosclerosis than seronegative individuals.
- ECs may benefit from cardiovascular management interventions.
- EC may also benefit from ART.
- Further research is needed on this topic to better assess the health implications of ECs.

A MATTER OF HEART POTENTIAL ATHEROSCLEROSIS RISK FACTORS IN THE HIV ELITE CONTROLLER POPULATION

